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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,349	SEID, ROBERT	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32 and 43-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31, 32 and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

Response to Applicant's Amendment

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 01/03/05 in response to the non-final Office Action mailed 09/30/04. With this, Applicant has amended the specification.

Status of Claims

2) Claims 48 and 49 have been canceled via the amendment filed 01/03/05.

Claims 31, 32, 44 and 47 have been amended via the amendment filed 01/03/05.

Claims 31, 32 and 43-47 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the title made in paragraph 5 of the Office Action mailed 09/30/04 is withdrawn in light of Applicant's amendment to the title.

6) The objection to the title made in paragraph 6(a) of the Office Action mailed 09/30/04 is withdrawn in light of Applicant's amendment to the specification.

7) The objection to the title made in paragraph 6(b) of the Office Action mailed 09/30/04 is withdrawn in light of Applicant's amendment to the specification.

8) The objection to the title made in paragraph 6(c) of the Office Action mailed 09/30/04 is withdrawn in light of Applicant's amendment to the specification.

Rejection(s) Moot

9) The rejection of claims 48 and 49 made in paragraphs 10(a), 10(f) and 10(i) of the Office

Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicant's cancellation of the claims.

10) The rejection of claims 48 and 49 made in paragraphs 14 of the Office Action mailed 09/30/04 under 35 U.S.C. § 103(a) as being unpatentable over Jennings *et al.* (US 5,811,102 - Applicants' IDS) ('102) as applied to claims 31 or 32 above, and further in view of Sato *et al.* (*J. Biol. Chem.* 270 (32): 18923-18928, 1995 - Applicant's IDS) and Staveski *et al.* (US 5,354,853 - Applicant's IDS), is moot in light of Applicant's cancellation of the claims.

11) The rejection of claims 48 and 49 made in paragraph 8 of the Office Action mailed 09/30/04 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of the U.S. Patent 6,638,513, is moot in light of Applicant's cancellation of the claims.

Rejection(s) Maintained

12) The rejection of claims 31, 32 and 43-47 made in paragraph 8 of the Office Action mailed 09/30/04 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of the U.S. Patent 6,638,513, is maintained for reasons set forth therein and herebelow. Applicant requests that the requirement for submission of a Terminal Disclaimer be held in abeyance until there is an indication of allowable subject matter in the present application.

Rejection(s) Withdrawn

13) The rejection of claims 31, 32, 44 and 47 made in paragraph 10(a) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

14) The rejection of claims 31, 32 and 47 made in paragraph 10(b) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

15) The rejection of claims 31 and 32 made in paragraph 10(c) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

16) The rejection of claims 31 and 32 made in paragraph 10(d) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

17) The rejection of claims 31 and 32 made in paragraph 10(d) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

18) The rejection of claims 31 and 32 made in paragraph 10(f) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

19) The rejection of claim 47 made in paragraph 10(g) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the base claim.

20) The rejection of claims 31, 32 and 43-47 made in paragraph 12 of the Office Action mailed 09/30/04 under 35 U.S.C. § 102(e)(2) as being anticipated by Jennings *et al.* (US 5,811,102 - Applicant's IDS) ('102) is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

21) The rejection of claim 31 made in paragraph 10(h) of the Office Action mailed 09/30/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn upon further consideration.

Response to Applicant's Arguments on 35 U.S.C. § 103 Rejection

22) Applicant cites MPEP 2143.03 and contends that all the claim limitations must be taught or suggested by the prior art to support an obviousness rejection under 35 U.S.C. § 103. Applicant further cites MPEP 706.02 and states that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. Applicant alleges that the cited combination is based on impermissible hindsight reconstruction, and that the Office has not presented a *prima facie* case of obviousness. Applicant cites *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) and states that one

cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

With regard to the teachings of Jennings *et al.* ('102), Applicant states that: (a) Jennings *et al.* ('102) do not teach or disclose a glycoconjugate comprising a covalently attached C3-C16 long-chain aliphatic lipid; (b) Jennings *et al.* ('102) do not disclose the preparation of glycoconjugates having substantially homogeneous sized MenB OS wherein the average degree of polymerization of the MenB OS is 10-20 or 12-18.

With regard to the teachings of Sato *et al.*, Applicant states that Sato *et al.* describe some oligosaccharide-lipid conjugates, but the oligosaccharides in the conjugates are structurally different from MenB OS. Applicant contends that Sato *et al.* fail to describe glycoconjugates comprising MenB OS, nor provide any incentive for using MenB OS, and therefore the teachings of Sato *et al.* are not applicable to the present invention.

With regard to the teachings of Staveski *et al.*, Applicant states that Staveski *et al.* disclose phospholipid-saccharide conjugates and their use to produce liposomes, but do not provide any incentive to use the claimed MenB OS glycoconjugates as claimed.

Applicant's arguments have been carefully considered, but are non-persuasive. If Jennings *et al.* ('102), Sato *et al.* and Staveski *et al.* taught every limitations of the instant claims, then these references would have been applied as anticipatory references under 35 U.S.C. § 102 as opposed to 35 U.S.C. § 103. If Sato *et al.* described oligosaccharide-lipid conjugates that are structurally different from MenB OS, the reference of Sato *et al.* would have been applied as an anticipatory reference under 35 U.S.C. § 102. As set forth below under paragraph 25, the teachings or suggestion to make the claimed glycoconjugate product and the reasonable expectation of success both are found in the cited prior art references and did not come from Applicant's disclosure.

It should be noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Sato *et al.* expressly taught a method of conjugating a phospholipid specifically to oligosaccharides of alpha (2->8)-linked polysialic acid with defined degrees of polymerization (Dp). Jennings' MenB oligosaccharide chemically contains alpha (2->8)-linked

polysialic acid with defined degrees of polymerization (Dp). Sato *et al.* and Staveski *et al.* also taught the advantage of such a conjugation. Further, with regard to Applicant's allegation of hindsight reconstruction, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Absent evidence that an alpha (2->8) linked polysialic acid-containing compound of a defined DP, such as Jennings' ('102), would not serve as a beneficial liposome preparation on conjugating to Sato's or Staveski's phosphatidylethanolamine, the rejection stands.

Applicant appears to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the claimed glycoconjugate is obvious over the prior art glycoconjugate, given the teaching of the applied prior art references. As explained above, the invention as a whole, would have been *prima facie* obvious to a practitioner in view of the knowledge in the art at the time of invention, the state of the art at the time of the invention, and the combined teachings of Jennings *et al.* ('102), Sato *et al.*, and Staveski *et al.* Applicant has provided no evidence within the instant specification to demonstrate that the claimed glycoconjugate differs in any unexpected or unobvious manner from that which one of ordinary skill in the art would have expected to obtain upon combining the teachings of the cited references. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, the cited references provide sufficient reason, suggestion, or motivation to combine their teachings. The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability (see *In re Lamberti*, 192 USPQ

278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

23) Claim 31 and those that are dependent therefrom are rejected under 35 U.S.C. § 112, second paragraph, as being containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

Claim 31, as amended, include the new step added as step (c): 'covalently attaching a C3-C16 long-chain aliphatic lipid to the nonreducing end of the MenB OS'. Applicant states that page 14, line 16 through page 16, line 33 describe methods of preparing glycoconjugates with covalently attached lipids. However, a review of the specification indicates that these portions of the specification are limited to a specific MenB OS glycoconjugate, 'CONJ-4', comprising substantially homogeneous sized N-propionylated MenB OS having a C3-C16 long-chain aliphatic lipid covalently attached to the non-reducing end of the N-propiolylated MenB OS and being conjugated to a protein carrier. These portions of the specification do not describe a glycoconjugate as recited in the amended claim 31 comprising MenB OS having N-acetyl groups replaced with 'N-acyl groups' as recited broadly wherein the MenB OS is covalently attached to a generic 'carrier molecule'. The scope of the terms 'N-acyl groups' and 'a carrier molecule' is not the same as the scope of the terms 'N-propionyl groups' and 'a protein carrier' respectively. Therefore, the limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to remove the new matter from the claim(s), or point to specific page and line numbers in the specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

24) Claims 31, 32 and 43-47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 31 is indefinite, confusing, and internally inconsistent in terms of scope, in the recitations: 'A glycoconjugate produced by a method' in line 1 of the claim and 'to provide a MenB OS glycoconjugate' at the end of the claim. What is obtained at the end of step (d) of the recited method is not a generic 'glycoconjugate', but a specific MenB OS glycoconjugate. In order to maintain the scope of the claim internally consistent, it is suggested that Applicant replace the limitation in line 1 of the claim with --A substantially homogeneous sized *Neisseria meningitidis* serogroup B capsular oligosaccharide (MenB OS) produced by a method--. The recitation in part (a) of the claim '*Neisseria meningitidis* serogroup B capsular oligosaccharide (MenB OS)' should be replaced with --MenB OS--. The limitations in lines 2 and 3 of step (e) of the claim: 'to provide a MenB OS glycoconjugate comprising substantially homogeneous sized MenB OS' should be replaced with the limitations: --to provide the substantially homogeneous sized MenB OS glycoconjugate--.

(b) Analogous criticism applies to claim 32.

(c) Claims 31 and 32 are vague, indefinite and confusing in the recitation: 'the MenB OS' in step (c) of the claims, because it is unclear which 'MenB OS' provides antecedent basis for the limitation. Whether or not antecedence for the limitation comes from MenB OS from step (a) or step (b) of the claims is not understood. Is the C3-C16 long-chain aliphatic lipid recited in step (c) being attached to 'the MenB OS' from step (a) or (step (b)?

(d) In step (d) of claims 31 and 32, for proper antecedent basis, it is suggested that Applicants replace the limitation: 'single end-activated MenB OS' with the limitation --single end-activated MenB OS of said Dp--.

(e) Claim 43, which depends from claim 31, is confusing, incorrect and/or has improper antecedence in the limitation: 'the reactive group introduced in step (c)', because step (c) of claim 31 does not recite any 'reactive group'.

(f) Claims 43-47, which depend directly or indirectly from claim 31, are also rejected

as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 103

25) Claims 31, 32 and 43-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jennings *et al.* (US 5,811,102 - Applicants' IDS) ('102) in view of Sato *et al.* (*J. Biol. Chem.* 270 (32): 18923-18928, 1995 - Applicant's IDS) and Staveski *et al.* (US 5,354,853 - Applicant's IDS).

The reference of Jennings *et al.* ('102) is applied in this rejection, because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

Jennings *et al.* ('102) taught a glycoconjugate comprising *Neisseria meningitidis* serogroup B capsular polysaccharide fragment derivatives in which sialic acid N-acetyl groups are replaced with N-propionyl groups (i.e., MenB OS) wherein such oligosaccharide derivatives are covalently attached to a carrier molecule, such as, tetanus toxoid (see Example 8). A method of producing the glycoconjugate is taught. The protein carrier in the glycoconjugate is CRM_{197} (see the sentence bridging columns 5 and 6). The conjugate was synthesized essentially as previously described and under the exact same conditions, i.e., as described in the preceding parts of the patent (see Example 8). The synthetic process and conditions are described elsewhere in the patent. The average molecular weight of the MenB oligosaccharide derivative was about 10 to 200 sialic acid residues (see column 5, lines 32-35), which encompasses the MenB OS having an average Dp of about 12 to18, or about 10 to 20 recited in the instant claims. Such materials were obtained using art known gel filtration or sizing membranes (see column 5, third paragraph). The N-propionylated MenB-tetanus toxoid conjugate disclosed in Example 8 contains modified polysaccharide fragments 'of the same molecular weight' (i.e., substantially homogenous sized MenB OS). The MenB oligosaccharide was conjugated to the carrier protein through a single binding site at the terminal end of the backbone of the oligosaccharide (see column 6, first and third full paragraphs).

The teachings of Jennings *et al.* ('102) have been explained above, which do not disclose the glycoconjugate comprising a C3-C16 long-chain aliphatic lipid covalently attached thereto at

the non-reducing end.

However, Sato *et al.* taught a method of conjugating by reductive amination an aliphatic lipid, phosphatidylethanolamine, to oligosaccharides of alpha (2->8)-linked polysialic acid (i.e., chemical equivalents of serogroup B meningococcal capsular oligosaccharides) with defined degrees of polymerization or Dp (see abstract and page 18924). It is disclosed that lipidated oligosaccharides do show retention of the immunological epitope (see page 18927).

Staveski *et al.* disclosed a method of coupling a phospholipid such as phosphatidylethanolamine (i.e., an aliphatic lipid) to an oligosaccharide to produce a novel phospholipid-saccharide conjugate (see abstract, column 3, lines 10-0, 45 and 46, and column 4, lines 43-50). Staveski *et al.* further taught that such conjugates can be used to produce liposomes (see column 4, lines 11 and 12).

Since the techniques of conjugating lipids to a saccharide, specifically to an oligosaccharide of alpha (2->8)-linked polysialic acid, were well known in the art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to attach Staveski's or Sato's aliphatic lipid, phosphatidylethanolamine, to Jennings' (102) substantially homogeneous sized N-propionylated serogroup B meningococcal capsular oligosaccharide glycoconjugate using Staveski's or Sato's method to produce the glycoconjugate of the instant invention, with a reasonable expectation of success. Given that lipidation of oligosaccharides was routinely practiced in the art for the purpose of production of liposomes as taught by Staveski *et al.*, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of using Jennings' ('102) conjugate, advantageously, as a liposome preparation, for the purpose of further increasing the immunogenicity of the conjugate.

Instant claims are product-by-process claims and are not limited to the manipulations of the recited steps, but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicant has not shown that the

alleged differences in the process result in a product that is structurally different from the product of the prior art.

Claims 31, 32 and 43-47 are *prima facie* obvious over the prior art of record.

Remarks

26) Claims 31, 32 and 43-47 stand rejected.

27) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (571) 273-8300.

28) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

29) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER